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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,046	11/20/2001	Frederic J. de Sauvage	P1405R1C1	1433

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GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/22/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/990,046	DE SAUVAGE ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,30,36-40,46-49 and 52-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,30,36-40,46-49 and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 10/4/06 has been entered.

Status of Application, Amendments and/or Claims

The amendment of 10/4/06 has been entered in full. Claims 29, 39 and 49 are amended. Claims 31-35, 41-45, 50 and 51 are canceled (claims 1-28 were previously canceled by Applicants). No new claims are added.

Claims 29, 30, 36-40, 46-49 and 52-54 are under consideration in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (4/5/2006).

All rejections of claims 31-35, 41-45, 50 and 51 are moot in view of Applicants' cancellation of these claims.

The rejection of claims 29, 30, 36-40, 46-49 and 52-54 under 35 U.S.C. § 112, first paragraph at pg 3-4 for containing new matter is *withdrawn* in view of Applicants' amendments to the claims that remove the language relating to "a polyclonal antibody that specifically binds" and conservative substitutions of 1 to 5 amino acids.

The rejection of claims 29, 30, 36-40, 46-49 and 52-54 under 35 U.S.C § 112, second paragraph, at pg 4-5 for being indefinite is *withdrawn in part* in view of

Applicants' amendments to the claims. Specifically, the grounds of rejection related to "and (2) which binds to..." and "conservatively substituted, added or deleted amino acid" are withdrawn in view of Applicants' amendments that remove these phrases from the claims. However, the grounds of rejection related to the term "specifically" being a relative term is maintained (see below). New grounds for rejection under 35 U.S.C § 112, second paragraph are also set forth below.

The rejection of claims 29, 39 and 49 under 35 U.S.C. 103(a) at pg 7-9 as being unpatentable over Motoyama (1998) in view of Liddell (1995) is *withdrawn* in view of Applicants' amendments to the claims that limit the claims to monoclonal antibodies.

Claim Objections

Claims 29, 30 and 40 are objected to because of the following informalities:

(1) Claim 29 is objected to because the term "hedgehog" is not italicized. The claims use the terms "*patched-2*" and "*Smoothened*". For consistency, "hedgehog" should be written "*hedgehog*" in the claims. It is noted that the term is italicized on page 1, line 18 of the specification.

(2) Claims 30 and 40 are objected to because "patched-2" is not italicized as in the parent claims from which they depend (i.e., claims 29 and 39 recite "*patched-2*")

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

Claim 49 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel biological materials; specifically claim 49 recites "...the patched polypeptide encoded by the human cDNA insert of the polynucleotide deposited under ATCC 209779" (emphasis added by examiner). Since the biological materials are essential to the claimed invention they must be obtainable

by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C § 112 may be satisfied by a deposit of the biological materials. It is noted that both the original specification (filed 11/20/01; pg 51) and the substitute specification (filed 4/15/05; pg 49) contain information on "Deposit of Material". However, the ATCC number of the deposit referred to in each case is ATCC 209778. Therefore, while the statement in the specification contains all of the required statements regarding a deposit regarding ATCC 209778, this does not provide enablement for deposit of ATCC 209779 as recited in claim 49.

It is noted that the originally filed claims (12/20/2001) referred to ATCC 209778 in claims 2 and 3. However, the preliminary amendment to the claims (also filed 12/20/2001) referred to ATCC 209779 in claim 49.

Claim Rejections - 35 USC § 112, 2nd paragraph

Claims 29, 30, 26-40 and 46-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "specifically" in claims 29, 39 and 49 is a relative term which renders the claim indefinite. The term "specifically" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The genus of proteins that are bound by the claimed antibody are rendered indefinite by the use of the term "specifically". This rejection was set forth at pg 4-5 of the 4/5/06 Office Action.

In the response dated 10/4/06, Applicants argue that the specification teaches monoclonal antibodies that bind to patched-2 and techniques for measuring the binding specificity including immunoprecipitation, radioimmunoassay and ELISA. Applicants argue "immunoprecipitation" is a process of precipitating an antigen from cell extracts using a specific antibody; "radioimmunoassay" is a process of determining the amount

of labeled antigen in a solution using a specific antibody; and that ELISA is a technique using a specific antibody in conjunction with a secondary antibody. Applicants argue that one of ordinary skill in the art would know that antibody "binding specificity" means that an antibody that binds to one antigen and only to that antigen. Applicants argue that the recited techniques make it unambiguously clear that the Applicants' intended definition of specificity is consistent with that used in the enumerated techniques, which is an antibody that binds only to a single antigen. Applicants further argue that "binding affinity" is introduced as a distinct concept in the specification from "binding specificity".

Applicants' arguments have been fully considered but are not found persuasive. Binding affinity is a measure of the strength of the binding between a particular antibody and its ligand, which is a specific epitope on a protein. Binding affinity is not an issue here. Rather, the issue is determining which proteins are included in the genus of proteins to which the claimed antibody "specifically binds". With regard to the instant application, the prior art teaches a mouse patched-2 protein with approximately 90% identity to instant SEQ ID NO: 2, including numerous regions of 20 or more amino acids with 100% identity. This degree of identity indicates that the genus of monoclonal antibodies that bind mouse patched-2 has a high degree of overlap with the genus of monoclonal antibodies that bind to SEQ ID NO: 2. The regions of exact identity contain epitopes that generate monoclonal antibodies that would bind to either protein, particularly if the proteins are denatured and presented in linear form. Applicants argue that one of ordinary skill in the art would recognize that the term "specifically binds" includes antibodies that can bind to a particular protein (e.g., SEQ ID NO: 2) but excludes those antibodies that can bind to another protein (e.g., mouse patched-2). However, Applicants have provided no evidence, such as publications from the relevant literature, supporting this assertion. While the specification teaches techniques (immunoprecipitation, radioimmunoassay, ELISA) to determine "binding specificity", this does not clearly define what is included or excluded by the term "specifically binds". For example, a monoclonal antibody that binds to an identical epitope in each of mouse patched-2 and SEQ ID NO: 2 would be considered to be specific for each of these

proteins, and non-specific for other proteins. Therefore, the examiner maintains that the term "specifically binds" is indefinite, as the specification does not clearly define what is included or excluded by the term. For purposes of prosecution, it is maintained that the claims encompass antibodies that bind to identical epitopes found in other proteins.

The following new grounds for rejection under 112, 2nd paragraph are added.

Claim 29 is also indefinite because the phrase "binds to hedgehog polypeptide" refers to a specific polypeptide, but the specific polypeptide is not clear. The term "hedgehog polypeptide" encompasses the *hedgehog* polypeptide from *Drosophila melanogaster*, as well as any vertebrate hedgehog polypeptides such as *Sonic hedgehog*, *Desert hedgehog*, *Indian hedgehog* and *Tiggie-winkle hedgehog*. In this regard, claim 29 would be rendered definite if amended, for example, to recite "...binds to a hedgehog polypeptide". This would clarify that the claim refers to a genus of hedgehog polypeptides rather than just a single specific hedgehog polypeptide.

Claims 29 and 39 are indefinite because it is not clear whether the term "a variant thereof" refers to "a purified monoclonal antibody" or "a *patched-2* polypeptide of SEQ ID NO: 2". In this regard, the claims would be rendered definite if amended, for example, to recite "...a variant of said polypeptide..."

Claims 29 and 39 are indefinite for reciting "a variant having at least about 95% sequence identify". MPEP 2173.05(b) ("Relative Terminology") states "claims reciting "at least about" were invalid for indefiniteness where there was close prior art and there was nothing in the specification, prosecution history, or the prior art to provide any indication as to what range of specific activity is covered by the term "about." In the instant case, the prior art (Motoyama, 1998, cited previously) teaches a mouse patched-2 polypeptide that is 89.3% similar to instant to the human patched-2 polypeptide SEQ ID NO: 2. Due to the high degree of similarity between the human and murine hedgehog pathways, and the fact that human *patched-2* protein can bind several murine hedgehog polypeptides, the *patched-2* protein from mice would inherently have the characteristic of binding to a hedgehog or a *Smoothened* polypeptide. Therefore, it is unclear whether the polypeptide taught by Motoyama is encompassed by the term "at least about 95%"

used in claims 29 and 39. For purposes of prosecution, the term will be interpreted to encompass the murine *patched*-2 protein taught by Motoyama.

Claim 39 is also indefinite because the phrase "binds to *Smoothened* polypeptide" refers to a specific polypeptide, but the specific polypeptide is not clear. The term "*Smoothened* polypeptide" encompasses the *Smoothened* polypeptide from *Drosophila melanogaster*, as well as any vertebrate *Smoothened* polypeptides. In this regard, claim 29 would be rendered definite if amended, for example, to recite "...binds to a *Smoothened* polypeptide". This would clarify that the claim refers to a genus of *Smoothened* polypeptides rather than just a single specific *Smoothened* polypeptide.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 103

Claims 29, 30, 36-40, 46-49 and 52-54 are rejected under 35 U.S.C. 103(a) Claims 29-33, 35-43, 45-49 and 51-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motoyama et al. (18 February 1998. Nat Genet. 18(2): 104-6) in view of Tso et al (U.S. Patent No. 5,932,448, published 3 August 1999, and filed 11/29/1991). This rejection was set forth previously and maintained at pg 5-9 of the 4/5/06 Office Action.

In the 10/4/06 response, Applicants argue, "neither Motoyama nor Tso *et al* disclose antibodies that specifically binding to USP 5,932,448" (pg 11). Applicants request reconsideration and withdrawal of the rejection of the claims.

Applicants' arguments have been fully considered but are not found persuasive. The meaning of "specifically binding to USP 5,932,448" is not clear. USP 5,932,448 is a U.S. Patent titled "Bispecific antibody heterodimers". However, the examiner assumes this is a typographical error and that Applicants intended to refer to "specifically binding to SEQ ID NO: 2". In response, the Examiner maintains that Motoyama in view of Tso do render obvious antibodies that specifically bind to instant SEQ ID NO: 2.

As amended, claims 29, 30, 39, 40 and 49 each encompass a monoclonal antibody that specifically binds to a patched-2 polypeptide of instant SEQ ID NO: 2 or

variants of SEQ ID NO: 2 that are at least 95% identical and bind to a *hedgehog* or *Smoothened* polypeptide. The remaining claims depend from claims 29, 29, 39 or 49 and limit the antibodies to those that are humanized (claims 36, 46 and 52), bispecific (claims 37, 47 and 53), or heteroconjugated (claims 8, 48 and 54).

Motoyama teaches the mouse gene *Ptch2* that encodes the polypeptide patched-2. The sequence of the mouse patched-2 polypeptide is 89.3% similar to instant SEQ ID NO: 2 (which is the human patched-2 polypeptide). An alignment of the two sequences was attached to the 7/12/05 Office Action as Sequence Alignment #1. Motoyama does not teach an antibody to the mouse patched-2 polypeptide.

Tso teaches general methods for producing bispecific antibodies (col 1, line 62-67). Tso further teaches monoclonal antibodies for use in production of bispecific antibodies (col 7, line 19). Tso further teaches humanized antibodies for use in bispecific antibodies (col 2, lines 46-47). The instant specification defines heteroconjugated antibodies as "antibodies composed of two covalently joined antibodies (pg 26). Tso teaches chemical cross-linking of two antibodies to produce a bispecific antibody (col 1, lines 34-35). This bispecific antibody taught by Tso meets the definition of a "heteroconjugated" antibody as defined by the specification.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make antibodies as taught by Tso to the mouse patched-2 polypeptide taught by Motoyama. The person of ordinary skill in the art would be motivated to do so because Tso teaches that the antibodies have general uses applicable for use with any protein, such as cross-linking a horseradish peroxidase for purposes of detection (see col 11, lines 52-55). The person of ordinary skill in the art would have expected success because Motoyama teaches the sequence of mouse patched-2 polypeptide, and Tso teaches the methods necessary to produce antibodies to any protein sequence.

Such antibodies are encompassed by the instant claims for two reasons:

(1) Due to the high degree of similarity between the two sequences, including numerous regions of 20 or more amino acids with 100% identity between the

sequences, one of skill in the art would reasonably predict that numerous monoclonal antibodies (including bispecific, humanized, or heteroconjugated antibodies) made to mouse patched-2 polypeptide as taught by Motoyama would specifically bind to the human patched-2 polypeptide of instant SEQ ID NO: 2. As set forth in the section, "Claim Rejections - 35 U.S.C. 112, 2nd Paragraph", the term "specifically binds" is not clearly defined in the specification as excluding antibodies that bind to other proteins (e.g., mouse patched-2). Therefore, as many of the monoclonal antibodies to mouse patched-2 would also bind to instant SEQ ID NO: 2, the teachings of Motoyama in view of Tso render obvious the antibodies encompassed instant claims.

(2) As amended, the instant claims encompass monoclonal antibodies that bind to variants of SEQ ID NO: 2 that have "at least about 95% sequence identity" and bind to a *hedgehog* or *Smoothened* polypeptide. 2. As set forth in the section, "Claim Rejections - 35 U.S.C. 112, 2nd Paragraph", the term "at least about" is indefinite in view of an absence of a teaching in the specification regarding the range encompassed by the term "about". MPEP 2173.05(b) ("Relative Terminology") states "claims reciting "at least about" were invalid for indefiniteness where there was close prior art and there was nothing in the specification, prosecution history, or the prior art to provide any indication as to what range of specific activity is covered by the term "about." Furthermore, due to the high degree of similarity between the human and murine hedgehog pathways, and the fact that human *patched-2* protein can bind several murine hedgehog polypeptides, the *patched-2* protein from mice would inherently have the characteristic of binding to a *hedgehog* or a *Smoothened* polypeptide. Therefore, the term "at least about 95% sequence identity" as applied to instant SEQ ID NO: 2 has been interpreted to encompasses the sequence of the mouse patched-2 protein. Therefore, monoclonal antibodies to mouse patched-2 are rendered obvious by the teachings of Motoyama in view of Tso.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER